EU RMP	
Drug Substance	Eplontersen Sodium
Version Number	1
Succession Number	4
Data lock point	07 April 2023
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for WAINZUA™ (EPLONTERSEN)

The content of this RMP has been reviewed and endorsed by the QPPV

[redacted]

Administrative Information

Rationale for submitting an updated RMP

Not applicable for initial marketing authorisation.

Summary of significant changes in this RMP

Not applicable, Version 1.

TABLE OF CONTENTS

LIST OF ANNEXES

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
2′-MOE	2′-*O*-methoxyethyl
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ASO	Antisense oligonucleotide
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATTReuNET	European Network for TTR-FAP
ATTRv	Hereditary transthyretin-mediated amyloidosis
ATTRv-CM	Hereditary transthyretin-mediated amyloidosis with Cardiomyopathy
ATTRv-PN	Hereditary transthyretin-mediated amyloidosis with Polyneuropathy
AUC	Area under the curve
EEA	European Economic Area
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EU RMP	European Union Risk Management Plan
GalNAc	*N*-acetyl galactosamine
Gapmer	Type of oligonucleotide that has a deoxynucleotide core sequence flanked on both ends with modified-nucleotide sequences
GI	Gastrointestinal
HbA1C	Hemoglobin A1C
hERG	human Ether-à-go-go-related gene
HIV	Human immunodeficiency virus
INN	International Non-proprietary Name
IST	Investigator-sponsored Trial
LICA	Ligand-conjugated antisense oligonucleotide
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
NIS	Neuropathy impairment score
NYHA	New York Heart Association
OAEI	Other adverse event of interest
P25	25th percentile

Abbreviation/ Special term	Definition/Explanation
P75	75th percentile
PIL	Patient Information Leaflet
PLT	Platelet
PSUR	Periodic Safety Update Report
PT	(MedDRA) Preferred Term
Q	Quarter
q4wk	Every 4 weeks
RBP4	Retinol binding protein 4
RMP	Risk Management Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA query
TEAE	Treatment-emergent adverse event
TSH	Thyroid stimulating hormone
TTR	Transthyretin
ULN	Upper limit of normal
Val30Met	Valine to methionine at position 30

I. PART I: PRODUCT OVERVIEW

Table I-1 Product Overview

Active substance(s) (INN or common name)	Eplontersen
Pharmacotherapeutic group(s) (ATC Code)	OTHER NERVOUS SYSTEM DRUGS (N07XX21)
Marketing Authorisation Applicant	AstraZeneca AB
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	WAINZUA
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Eplontersen is an ASO
	Summary of mode of action: Eplontersen is a GalNAc conjugated 2′-MOE-modified chimeric gapmer ASO with a mixed backbone of phosphorothioate and phosphate diester internucleotide linkages. The GalNAc conjugate enables targeted delivery of the ASO to hepatocytes. The selective binding of eplontersen to the Transthyretin (TTR) mRNA within the hepatocytes causes the degradation of both mutant and wild-type (normal) TTR mRNA. This prevents the synthesis of TTR protein in the liver, resulting in significant reductions in the levels of mutated and wild-type TTR protein secreted by the liver into the circulation.
Hyperlink to the Product Information	WAINZUA Summary of Product Characteristics
Indications in the EEA	Current: WAINZUA is indicated for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv).
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose of WAINZUA is 45 mg administered by subcutaneous injection. Doses should be administered monthly.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths in the EEA	Current: Solution for injection in pre-filled pen. Each pre-filled pen contains 45 mg eplontersen (equivalent to 47 mg eplontersen sodium) in 0.8 mL solution.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

II. PART II: SAFETY SPECIFICATION

II.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Incidence

Within Europe, the incidence of ATTRv is highly variable and there are large areas in Portugal and northern Sweden where the disease is endemic (Skrahina et al 2021, Samuelsson et al 2022). In the rest of Europe, ATTRv is generally thought to be sporadic (Parman et al 2016).

Reported incident cases of ATTRv from medical records in Norrbotten, Sweden, between 2006 and 2018, suggest an overall incidence rate of 28.6 cases per 1,000,000 person years, with higher incidence rates reported for men than women (38.7 versus 18.2 cases, respectively). The overall incidence rate of ATTRv per 1,000,000 person years increased from 15 cases between 2006 to 2009 to 49.2 cases between 2016 to 2018. Within the same time period, the standardised mortality rate in the ATTRv cohort was estimated to be 2.64 times higher than in the general population (Mejia Baranda et al 2022).

Polyneuropathy Associated with Hereditary Transthyretin-mediated Amyloidosis

In Europe, the incidence of ATTRv-PN is estimated to be between 0.3 to 10 cases per 1,000,000 person years (with counts of between 5,000 and 6,000 patients) (EMA 2022).

Data from the ATTReuNET questionnaire suggest that Portugal has the highest number of diagnosed symptomatic cases of ATTRv-PN (2,000 patients) and more than 500 diagnosed asymptomatic carriers of the disease (Table II-1) (Parman et al 2016, Schmidt et al 2018). Recent estimates of ATTRv-PN from Portugal between 2010 and 2016 suggest a mean incidence rate of 8.7 per 1,000,000 adults per year, corresponding to 71 new patients annually; 28.7% of these incident cases were late onset cases (age ≥ 50 years) (Inês et al 2018).

In some areas of new endemicity in Europe, such as Cyprus, an incidence of 3 per 1,000,000 person year has been reported for ATTRv-PN (Andreou et al 2018). Majorca, another new endemic area, reported 107 cases of ATTRv-PN between 2001 and 2012 (Reinés et al 2014).

Prevalence:

Hereditary Transthyretin-mediated Amyloidosis

In Europe, the overall prevalence of ATTRv is estimated to be less than 10 in 1,000,000 individuals (Ando et al 2013). Areas of new endemicity of ATTRv have been reported in Cyprus, with an estimated prevalence in 2016 of 54 per 1,000,000 individuals (Andreou et al 2018). In Portugal, in 2016, the estimated crude prevalence was 229.3 per 1,000,000 adults, corresponding to 1865 individuals with ATTRv, a 16% increase in

prevalence over the past 25 years (Inês et al 2018). In Sweden (Norrbotten area), in 2018, the prevalence of ATTRv was 251 per 1,000,000 people (Lindmark K et al 2021).

Among the nonendemic regions in Europe, France, Italy, and Germany have the highest number of confirmed cases of ATTRv. A prevalence of ATTRv-PN of 8.8 per 1,000,000 individuals has been reported in Sicily (Mazzeo et al 2015). Survey data from Lazio, Italy, a high prevalence region in a non-endemic country, identified 100 patients with ATTRv, corresponding to an estimated prevalence of 17.2 per 1,000,000 individuals (Luigetti et al 2021).National prevalence of ATTRv in Italy is reported to be 4.33 per 1,000,000 individuals (Russo et al 2020). In Greece, total number of ATTRv-PN patients diagnosed during the past 25 years is 57, mostly concentrated in the Island of Crete, corresponding to a national prevalence of ATTRv-PN outside of Crete of <0.1 per 1,000,000 individuals (Koutsis et al 2021); whilst in Crete prevalence of ATTRv reached 35 per 1,000,000 people (Tzagournissakis M et al 2022). ATTRv national prevalence has been estimated in several European countries, including Hungary at 2.35 per 1,000,000 individuals (Pozsonyi et al 2021), Austria at 5 per 1,000,000 individuals (Auer-Grumbach et al 2020), and Bulgaria at 5.68 per 1,000,000 individuals (Schmidt et al 2018).

Polyneuropathy Associated with Hereditary Transthyretin-mediated Amyloidosis

The worldwide population of patients with prevalent ATTRv-PN is estimated to reach between 10,000 and 50,000 patients (Gertz 2017, Schmidt et al 2018). There is a variable distribution of ATTRv-PN, with higher rates reported in Portugal and northern Sweden (Schmidt et al 2018). Estimates for EMA member states together with Iceland, Liechtenstein, and Norway were extracted from Schmidt et al 2018 and used as a basis for estimation of overall prevalence in the European Union (EU) for ATTRv-PN (Table II-1). The table below presents the national prevalence counts of ATTRv-PN across the EU either reported or extrapolated (from number of ATTRv-PN cases in countries where prevalence estimated were not provided) by Schimdt et al in 2018 (Table II-1).

Table II-1 Prevalence of ATTRv-PN across the European Union, Total and by Country (Reported and Extrapolated)

Country	General population, in Millions	Prevalence counts (low estimate-high estimate)	Source
Austria	8.6	13 (3-65)	Extrapolated
Belgium	11.3	17 (4-85)	Extrapolated
Bulgaria	7.2	41	Reported

Table II-1 Prevalence of ATTRv-PN across the European Union, Total and by Country (Reported and Extrapolated)

Country	General population, in Millions	Prevalence counts (low estimate-high estimate)	Source
Cyprus	1.2	51	Reported
Czech Republic	10.6	16 (3-79)	Extrapolated
Denmark	5.7	8 (2-43)	Extrapolated
Finland	5.5	8 (2-41)	Extrapolated
France	66.8	502	Reported
Germany	81.4	121	Reported
Greece	10.8	16 (3-81)	Extrapolated
Hungary	9.8	15 (3-74)	Extrapolated
Italy	60.8	550 (500-600)	Reported
Luxembourg	0.6	1 (0-4)	Extrapolated
Netherlands	16.9	45	Reported
Poland	38	56 (12-286)	Extrapolated
Portugal	10.3	2051 (1990-2111)	Reported
Romania	19.8	29 (6-149)	Extrapolated
Slovenia	2.1	3 (1-16)	Extrapolated
Spain	46.4	69 (15-349)	Extrapolated
Sweden	9.8	253	Reported
Total	**423.6**	**3865 (3557-4996)**	**Calculated**

Exact prevalence counts are reported whenever available, and alternatively midpoint of estimate of prevalence counts is reported alongside low and high estimate values.

Data adapted from Parman et al 2016, Schmidt et al 2018**.**

Demographics of the Population in the Proposed Indication and Risk Factors for the Disease:

Hereditary Transthyretin-mediated Amyloidosis

The age of onset of ATTRv varies between countries and among people carrying the same mutation. The age at onset of disease-related symptoms also varies across different populations.

The age of onset for ATTRv may vary depending on the predominantly affected system; the mean age at diagnosis of ATTRv with cardiomyopathy (ATTRv-CM) is around the sixth decade while ATTRv-PN is mostly diagnosed in the third to fifth decade of life (Coelho et al 2013). However, the prevalence of disease and age at diagnosis also widely vary geographically, with higher prevalence and younger ages of diagnosis in endemic areas, such

as Portugal, Spain, France, Japan, Northern Sweden, and descendants of these regions (Lindmark et al 2021, Luigetti et al 2020, Gertz 2017).

Polyneuropathy Associated with Hereditary Transthyretin-mediated Amyloidosis

The mean age of symptom onset is variable, with earlier onset observed among Portuguese patients with ATTRv-PN (mean age: 33 years; Sousa et al 1993) and later onset observed among Swedish patients with ATTRv-PN (mean age 56 years; Holmgren et al 1994).

Risk Factors

The inheritance pattern of ATTRv is autosomal dominant and therefore, assuming the affected individual is heterozygous for the pathogenic variant, the chance that the child of an affected individual will inherit the causative gene is 50% (American Heart Association 2022, Živkovic 2020). Geographical location is an important factor in the distribution of the disease as the prevalence of pathogenic TTR mutations, including variants known to be associated with the development of polyneuropathy, such as Val30Met, varies with region, leading to geographical clustering, such as in Portugal, in Sweden, and in Japan (American Heart Association 2022).

The Main Existing Treatment Options:

Current treatment options for ATTRv-PN include orthotopic liver transplant or silencing TTR production using either ASO therapy with inotersen or small interfering RNA therapy with patisiran or vutrisiran. These treatment options either have moderate efficacy, administration challenges, or are associated with safety issues. Tafamidis, a TTR tetramer stabiliser, is another treatment option for patients with Stage 1 ATTRv-PN.

Natural history of the indicated condition in the Untreated population, including mortality and morbidity:

ATTRv is a rare, under-recognised, debilitating, rapidly progressive, irreversible, and fatal disease with a typical life expectancy of 5 to 15 years after diagnosis (Zeldenrust 2010, Barreiros et al 2013, Hawkins et al 2015). Sensorimotor neuropathy leads to a loss of ambulatory function, and severe autonomic neuropathy impacts the cardiovascular, GI, and genitourinary systems, ultimately leading to declines in quality of life (Sekijima 2015, Aimo et al 2021).

The presentation and clinical course of ATTRv varies depending on the underlying TTR mutation and may lead to heterogenous disease presentations (Galant et al 2017, Planté-Bordeneuve and Said 2011, Thenappan et al 2014). The geographic origin and race of the patient can impact the onset and initial disease symptoms for a given mutation (Galant et al 2017, Tzagournissakis et al 2022, Wilczek et al 2011). In a majority of patients, the minimum age of systemic disease manifestation is 20 years and neurologic symptoms typically occur in patients between the age of 25 to 40 years (Hemming et al 1998, Bourque et al 2016).

The most common initial clinical presentation is the neurological complaint of loss of sensory function (disproportionally affecting sensation of pain and temperature), typically affecting the small myelinated and unmyelinated nerve fibres (Buades-Reinés et al 2016, Hund 2012, Planté-Bordeneuve et al 2007, Tzagournissakis et al 2022, Wilczek et al 2011). The sensory and motor deficits typically begin in the lower extremities and progress to proximal neuropathies within the following months to years. Ambulatory status is affected and walking without an aid becomes increasingly difficult (Planté-Bordeneuve and Said 2011). At later stages of the disease, larger fibres may be involved, leading to debilitating muscle weakness and atrophy (Hund 2012). The nerve length-dependent polyneuropathy may progress to life threatening autonomic dysfunction leading to urinary and GI dysfunction, erectile dysfunction, orthostatic hypotension, and, later, cachexia and death (Galant et al 2017, Planté-Bordeneuve and Said 2011).

Gastrointestinal symptoms include diarrhoea, severe constipation, alternating diarrhoea/constipation, vomiting and gastroparesis, all of which lead to progressive weight loss. Urinary symptoms and, in men, erectile dysfunction, may be present (Planté-Bordeneuve and Said 2011). Amyloid deposits in the kidney are common in patients with ATTRv regardless of the underlying genetic variant and can result in abnormal protein excretion, a common feature of the disease, as well as progression to renal failure (Ferraro et al 2021). Cardiac involvement has been estimated to occur in 80% of ATTRv-PN (Planté-Bordeneuve and Said 2011).

Morbidity and Mortality

For most TTR mutations, data on the expected survival are not available. Patients with the Val30Met mutation have been reported to have the best survival. Data gathered from various sources have suggested that the expected survival for patients with Val30Met mutation is between 9 to 15 years (Coelho et al 2018, Suhr et al 2016). Recent survival updates from the Familial Amyloidotic Polyneuropathy World Transplant Registry indicate that the 10-year survival varied markedly for the nine most common non-Val30Met mutations, ranging from 21% for the serine to arginine mutation at position 50, to 85% for the valine to alanine mutation at position 71. Poor survival was noted for all mutations with leptomeningeal complications except for those with the tyrosine to cysteine mutation at position 114 (Suhr et al 2016).

Patients typically die due to malnutrition and cachexia, renal failure, and cardiac disease (Coelho et al 2018).

Important co-morbidities:

ATTRv-associated comorbidities are similar to those that arise as part of the disease process and may include urinary and GI tract dysfunction, erectile dysfunction, orthostatic hypotension, neurogenic bladder, anaemia, weight loss, cardiac involvement such as thickened ventricular walls in the absence of hypertension, advanced atrio-ventricular block of unknown origin, and cachexia.

II.2 MODULE SII: NONCLINICAL PART OF CLINICAL PART OF THE SAFETY SPECIFICATION

Summary of key safety findings from nonclinical studies and relevance to human usage.

II.2.1 Toxicity

The nonclinical toxicology and pharmacokinetic evaluation of eplontersen included repeat dose studies up to 26 weeks (CD-1 mouse) and up to 39 weeks (cynomolgus monkey), a standard battery of genotoxicity studies, reproductive, and developmental toxicity study in mice, and a 26-week carcinogenicity study in hemizygous Tg.rasH2 transgenic mice. The potential consequences of reduction in TTR expression levels were assessed in the monkey where eplontersen is pharmacologically active. ION-1184986 (mouse-specific TTR inhibitor) was also included in the chronic study in mice to evaluate any potential toxicity associated with TTR inhibition with this particular chemical construct. In addition, the nonclinical toxicology programme for eplontersen included a single dose safety pharmacology study in the monkey (cardiovascular, neurobehavioral assessment, and respiratory) and *in vitro* hERG assay.

Key Issues Identified from Acute or Repeat-dose Toxicity Studies

The spectra of eplontersen-related findings observed in mice and monkeys were, in general, non-specific class effects that are typical for a 2′-MOE ASO (Henry et al 2008). The intended pharmacologic effect of dose dependent reduction in hepatic TTR mRNA levels (up to ~62% and 82% reductions) was achieved in monkeys and mice, respectively, and subsequent decreases in TTR plasma protein levels (up to 70% reduction) in monkeys. There were no toxicological findings considered related to the pharmacologic inhibition of TTR expression.

Key safety findings from toxicity studies and their relevance to human usage are provided in Table II-2.

Table II-2 Key Safety Findings from Toxicity Studies and Relevance to Human Usage

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Effects on Coagulation and Complement In the 13- and 39-week monkey studies, there was no clear evidence of acute, transient effects on activated partial thromboplastin time. The concentration of plasma complement split product Bb was elevated by eplontersen treatment in an acute, transient, and dose dependent- pattern, an effect that has also been described for several 2′-MOE ASOs in the monkey (Henry et al 1997, Farman and Kornbrust 2003). However, complement C3 levels were unaffected by eplontersen treatment at dose levels that were > 100-fold above the likely human exposure.	No evidence of alternative complement pathway activation was associated with eplontersen treatment in humans and no effects related to complement activation are expected in patients.
Reductions in Platelet Count The most noteworthy finding in the 13-week monkey study was a severely decreased PLT count in one of 12 monkeys in the high dose group (24 mg/kg/wk). No PLT reductions were observed in any other monkeys in the 24 mg/kg/wk dose group, in any of the remaining dose groups for 13 weeks, or in any other studies.	The low PLT count in this monkey is not attributed to either bone marrow toxicity or thrombosis. Importantly, the plasma AUC at 24 mg/kg/wk (96 mg/kg/month) in monkeys was > 100-fold higher than that for the clinical dose at 45 mg/month eplontersen.
Additional Treatment-related Effects Additional treatment-related effects were observed, including the presence of basophilic granules in the kidney, liver, and in resident macrophages in various tissues, particularly lymph nodes. The accumulation of basophilic granules in the liver of both mice and monkeys was associated with slight increases in liver weights at the high doses in the 13-week studies. However, there were no accompanying increases in serum ALT or abnormal hepatic morphology at exposure levels that were > 100-fold the proposed clinical doses.	The presence of basophilic granules is attributed to the uptake and accumulation of ASO in tissues. Nucleic acids, such as 2′-MOE ASOs (e.g., eplontersen) stain with haematoxylin and therefore their uptake into cells can be visualised microscopically as basophilic granules (Buades-Reinés et al 2016, Butler et al 1997). Thus, basophilic granules in tissue are indicative only of the presence of oligonucleotide in organs where compound exposure is the greatest (liver and kidney) and are not considered adverse in nature (Henry et al 2008).

Reproductive/Developmental Toxicity

The assessment of reproductive and developmental toxicity for eplontersen was conducted and showed no effects on fertility, pregnancy, and foetal development in mice. In addition, ION-1184986 treatment reduced liver TTR mRNA levels and did not produce any effects on fertility or embryo-foetal development in mice.

Antisense oligonucleotides, such as eplontersen, are not transported across the placenta because of their size, molecular charge, water solubility, and high plasma protein binding.

Genotoxicity

Eplontersen was not genotoxic in the bacterial reverse mutation assay, the chromosomal aberration assay in Chinese hamster lung cells, or the in vivo mouse bone marrow micronucleus assay.

Carcinogenicity

The carcinogenic potential of eplontersen was assessed in Tg.rasH2 transgenic mice for 26 weeks. Based on the findings and results, eplontersen did not produce any evidence of a carcinogenic effect in the CByB6F1 Tg(HRAS)2Jic hemizygous transgenic mouse model system.

II.2.2 Safety pharmacology

The nonclinical toxicology programme for eplontersen included a single-dose safety pharmacology study in the monkey (cardiovascular, neurobehavioral assessment, and respiratory) and in vitro hERG assay. There were no safety concerns identified for these organ systems in nonclinical studies.

II.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

Exposure to eplontersen is based on all patients who have received at least one dose of eplontersen in the pivotal study (ION-682884-CS3) or its long-term extension study (ION-682884-CS13) as of 07 April 2023 ('Eplontersen Treated Set'; N = 167). Within ION-682884-CS13, three patients originated from an investigator-sponsored trial (420915-CS101). These patients were treated with inotersen and subsequently directly enrolled into ION-682884-CS13 without participating in ION-682884-CS3. Only data collected in ION-682884-CS13 were included (i.e., data while on inotersen in Study 420915-CS101 are not included in the Eplontersen Treated Set). Tables presented in this section include cumulative data up to data cut-off (07 April 2023).

Additionally, safety evaluation based on the "Up to Week 66 data/Week 66 analysis" is presented in Section II.7.1, Section II.7.3 and Section VI.2.2. This analysis compares eplontersen data (hereafter referred to as "Eplontersen group"; N=144) from the pivotal study ION-682884-CS3 to the external placebo and the historical inotersen groups from the study ISIS 420915-CS2 with similar exposure across the treatment groups (for Week 66 analysis, Study Day 456 was applied as cut-off for each patient in the eplontersen, external placebo or historical inotersen groups).

Table II-3 Duration of Eplontersen Exposure (Eplontersen Treated Set)

Parameter **Group** **Summary/Category**
Duration of Study Drug Exposure (Days)[a]

Table II-3 Duration of Eplontersen Exposure (Eplontersen Treated Set)

Parameter **Group** **Summary/Category**		
Eplontersen Treated Set (N=167)[c]		
N	167	
Mean (SD)	627.7 (189.96)	
Median (P25, P75)	615.0 (556.0, 753.0)	
Minimum, Maximum	57, 1134	
Duration of Exposure	**Patients, n (%)**	**Person Time (Years)[b]**
Eplontersen Treated Set (N=167)[c]		
<6 months	3 (1.8)	0.68
>=6 months to <12 months	13 (7.8)	10.78
>=12 months to <24 months	102 (61.1)	161.53
>=24 months to <36 months	47 (28.1)	107.78
>=36 months to <48 months	2 (1.2)	6.20
Eplontersen 45 mg q4wk (N=144)[d]		
<6 months	3 (2.1)	0.68
>=6 months to <12 months	4 (2.8)	3.31
>=12 months to <24 months	89 (61.8)	144.96
>=24 months to <36 months	46 (31.9)	105.68
>=36 months to <48 months	2 (1.4)	6.20
Inotersen Prior to Switch/Eplontersen After Switch (N=20)[e]		
<6 months	0	NA
>=6 months to <12 months	8 (40.0)	6.77
>=12 months to <24 months	11 (55.0)	14.41
>=24 months to <36 months	1 (5.0)	2.10
>=36 months to <48 months	0	NA
IST Eplontersen q4wk (N=3)[f]		
<6 months	0	NA
>=6 months to <12 months	1 (33.3)	0.70
>=12 months to <24 months	2 (66.7)	2.16
>=24 months to <36 months	0	NA
>=36 months to <48 months	0	NA

[a] Duration of exposure was eplontersen last dose date minus eplontersen first dose date plus 1 day.

[b] Person time was the sum of eplontersen exposure time (years) for all patients in the category. Eplontersen exposure was calculated by the eplontersen last dose date minus eplontersen first dose date plus 1 day.

[c] Eplontersen Treated Set: Includes all patients who received at least 1 dose of eplontersen in the ION-682884-CS3 or ION-682884-C13 study.

[d] Includes all patients who received eplontersen from the beginning of ION-682884-CS3.

[e] Includes all patients who received inotersen initially in ION-682884-CS3 until Week 34, then switched to eplontersen at Week 37. Only data collected after the first dose of eplontersen were included (i.e., data through Week 36, while on inotersen before switch to eplontersen, are not included).

[f] Includes patients with a confirmed TTR mutation and evidence of polyneuropathy who completed the IST, Study 420915-CS101, with inotersen and directly enrolled into ION-682884-CS13 without participating in ION-682884-CS3.

Only data collected in ION-682884-CS13 were included (i.e., data while on inotersen in Study 420915-CS101 are not included).

For patients in ION- 682884- CS3 who continued into ION 682884-CS13, exposure data from ION-682884-CS13 are sequentially appended to their ION 682884 CS3 data.

[redacted]

Table II-4 Age Group and Gender (Eplontersen Treated Set)

Group / Age Group	Patients, n (%)			Person Time (Years)[a]		
	Male	Female	Total	Male	Female	Total
Eplontersen Treated Set (N=167)[b]						
Total	115 (68.9)	52 (31.1)	167 (100.0)	198.18	88.80	286.98
Children (<18 years)	0	0	0	NA	NA	NA
Adults (18-64 years)	82 (49.1)	32 (19.2)	114 (68.3)	143.05	57.10	200.15
Elderly people	33 (19.8)	20 (12.0)	53 (31.7)	55.13	31.70	86.83
65-74 years	29 (17.4)	15 (9.0)	44 (26.3)	49.74	24.41	74.15
75-84 years	4 (2.4)	5 (3.0)	9 (5.4)	5.39	7.29	12.68
>84 years	0	0	0	NA	NA	NA
Eplontersen 45 mg q4wk (N=144)[c]						
Total	100 (69.4)	44 (30.6)	144 (100.0)	181.42	79.42	260.84
Children (<18 years)	0	0	0	NA	NA	NA
Adults (18-64 years)	73 (50.7)	27 (18.8)	100 (69.4)	133.34	51.12	184.46
Elderly people	27 (18.8)	17 (11.8)	44 (30.6)	48.08	28.30	76.38
65-74 years	24 (16.7)	12 (8.3)	36 (25.0)	43.53	21.01	64.54
75-84 years	3 (2.1)	5 (3.5)	8 (5.6)	4.54	7.29	11.83
>84 years	0	0	0	NA	NA	NA
Inotersen Prior to Switch/Eplontersen After Switch (N=20)[d]						
Total	13 (65.0)	7 (35.0)	20 (100.0)	14.61	8.67	23.28
Children (<18 years)	0	0	0	NA	NA	NA
Adults (18-64 years)	8 (40.0)	5 (25.0)	13 (65.0)	8.71	5.97	14.69
Elderly people	5 (25.0)	2 (10.0)	7 (35.0)	5.90	2.70	8.60
65-74 years	4 (20.0)	2 (10.0)	6 (30.0)	5.05	2.70	7.75
75-84 years	1 (5.0)	0	1 (5.0)	0.85	NA	0.85
>84 years	0	0	0	NA	NA	NA
IST Eplontersen q4wk (N=3)[e]						
Total	2 (66.7)	1 (33.3)	3 (100.0)	2.16	0.70	2.86
Children (<18 years)	0	0	0	NA	NA	NA
Adults (18-64 years)	1 (33.3)	0	1 (33.3)	1.00	NA	1.00

Table II-4 Age Group and Gender (Eplontersen Treated Set)

Group Age Group	Patients, n (%)			Person Time (Years)[a]		
	Male	Female	Total	Male	Female	Total
Elderly people	1 (33.3)	1 (33.3)	2 (66.7)	1.16	0.70	1.86
65-74 years	1 (33.3)	1 (33.3)	2 (66.7)	1.16	0.70	1.86
75-84 years	0	0	0	NA	NA	NA
>84 years	0	0	0	NA	NA	NA

[a] Person time was the sum of eplontersen exposure time (years) for all patients in the category. Eplontersen exposure was calculated by the eplontersen last dose date minus eplontersen first dose date plus 1 day.

[b] Eplontersen Treated Set: Includes all patients who received at least 1 dose of eplontersen in the ION-682884-CS3 or ION-682884-C13 study.

[c] Includes all patients who received eplontersen from the beginning of ION-682884-CS3.

[d] Includes all patients who received inotersen initially in ION-682884-CS3 until Week 34, then switched to eplontersen at Week 37. Only data collected after the first dose of eplontersen were included (i.e., data through Week 36, while on inotersen before switch to eplontersen, are not included).

[e] Includes patients with a confirmed TTR mutation and evidence of polyneuropathy who completed the IST, Study 420915-CS101, with inotersen and directly enrolled into ION-682884-CS13 without participating in ION-682884-CS3.

Only data collected in ION-682884-CS13 were included (i.e., data while on inotersen in Study 420915-CS101 are not included).

For patients in ION-682884-CS3 who continued into ION-682884-CS13, exposure data from ION-682884-CS13 are sequentially appended to their ION-682884-CS3 data.

[redacted]

Table II-5 Ethnic Origin (Eplontersen Treated Set)

Ethnicity	Patients, n (%)	Person Time (Years)[a]
Eplontersen Treated Set (N=167)[b]		
Hispanic or Latino	26 (15.6)	39.85
Not Hispanic or Latino	139 (83.2)	243.11
Eplontersen 45 mg q4wk (N=144)[c]		
Hispanic or Latino	22 (15.3)	35.39
Not Hispanic or Latino	120 (83.3)	221.42
Inotersen Prior to Switch/Eplontersen After Switch (N=20)[d]		
Hispanic or Latino	4 (20.0)	4.45
Not Hispanic or Latino	16 (80.0)	18.83
IST Eplontersen q4wk (N=3)[e]		
Hispanic or Latino	0	NA
Not Hispanic or Latino	3 (100.0)	2.86

[a] Person time was the sum of eplontersen exposure time (years) for all patients in the category. Eplontersen exposure was calculated by the eplontersen last dose date minus eplontersen first dose date plus 1 day.

[b] Eplontersen Treated Set: Includes all patients who received at least 1 dose of eplontersen in the ION-682884-CS3 or ION-682884-C13 study.

[c] Includes all patients who received eplontersen from the beginning of ION-682884-CS3.

[d] Includes all patients who received inotersen initially in ION-682884-CS3 until Week 34, then switched to eplontersen at Week 37. Only data collected after the first dose of eplontersen were included (i.e., data through Week 36, while on inotersen before switch to eplontersen, are not included).

[e] Includes patients with a confirmed TTR mutation and evidence of polyneuropathy who completed the IST, Study 420915-CS101, with inotersen and directly enrolled into ION-682884-CS13 without participating in ION-682884-CS3.

Only data collected in ION-682884-CS13 were included (i.e., data while on inotersen in Study 420915-CS101 are not included).

For patients in ION-682884-CS3 who continued into ION 682884-CS13, exposure data from ION-682884-CS13 are sequentially appended to their ION 682884 CS3 data.

[redacted]

Table II-6 Race (Eplontersen Treated Set)

Race	Patients, n (%)	Person Time (Years)[a]
Eplontersen Treated Set (N=167)[b]		
Asian	24 (14.4)	42.98
Black or African American	5 (3.0)	10.07
White	131 (78.4)	223.46
Other	5 (3.0)	6.69
Multiple	1 (0.6)	1.54
Missing	1 (0.6)	2.25
Eplontersen 45 mg q4wk (N=144)[c]		
Asian	22 (15.3)	40.69
Black or African American	5 (3.5)	10.07
White	112 (77.8)	201.63
Other	3 (2.1)	4.67
Multiple	1 (0.7)	1.54
Missing	1 (0.7)	2.25
Inotersen Prior to Switch/Eplontersen After Switch (N=20)[d]		
Asian	2 (10.0)	2.29
Black or African American	0	NA
White	16 (80.0)	18.98
Other	2 (10.0)	2.02
Multiple	0	NA
Missing	0	NA
IST Eplontersen q4wk (N=3)[e]		
Asian	0	NA
Black or African American	0	NA
White	3 (100.0)	2.86
Other	0	NA
Multiple	0	NA
Missing	0	NA

[a] Person time was the sum of eplontersen exposure time (years) for all patients in the category. Eplontersen exposure was calculated by the eplontersen last dose date minus eplontersen first dose date plus 1 day.

[b] Eplontersen Treated Set: Includes all patients who received at least 1 dose of eplontersen in the ION-682884-CS3 or ION-682884-C13 study.

[c] Includes all patients who received eplontersen from the beginning of ION-682884-CS3.

[d] Includes all patients who received inotersen initially in ION-682884-CS3 until Week 34, then switched to eplontersen at Week 37. Only data collected after the first dose of eplontersen were included (i.e., data through Week 36, while on inotersen before switch to eplontersen, are not included).

[e] Includes patients with a confirmed TTR mutation and evidence of polyneuropathy who completed the IST, Study 420915-CS101, with inotersen and directly enrolled into ION-682884-CS13 without participating in ION-682884-CS3. Only data collected in ION-682884-CS13 were included (i.e., data while on inotersen in Study 420915-CS101 are not included).

For patients in ION-682884-CS3 who continued into ION-682884-CS13, exposure data from ION-682884-CS13 are sequentially appended to their ION-682884 CS3 data.

[redacted]

II.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

II.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Pregnant Patients

Reason for Exclusion:
Patients who are pregnant were excluded from participating in clinical trials to avoid potential harm to the unborn foetus.

Is It Considered To Be Included as Missing Information: Yes (Use in pregnant women and effects on pregnancy outcomes)

Lactating Patients

Reason for Exclusion:
There are no data on lactating patients. Patients who are lactating were excluded from participating in clinical trials to avoid potential harm to the breastfed infant.

Is It Considered To Be Included as Missing Information: No

Rationale:

It is not known whether eplontersen is excreted in human milk or has effects on the breastfed infant or milk production. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from eplontersen therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (SmPC Section 4.6). Although it is unknown whether eplontersen or its metabolites are excreted in human milk and a risk to the breastfed child cannot be excluded, it should be noted that ASOs possess poor oral bioavailability and poor passage into milk. Through poor oral bioavailability, coupled with the fact that the dose of eplontersen is very low relative to inotersen, no clinical impact on the breast-fed child from the carry-over of eplontersen in breast milk should be anticipated.

New York Heart Association Functional Classification of ≥ 3

Reason for Exclusion:
Patients with NYHA functional classification of ≥ 3 were excluded to avoid factors that may confound a complete understanding of the safety data of eplontersen and to ensure interpretability of the data.

Is It Considered To Be Included as Missing Information: No

Rationale:
Based on the evaluation of the clinical trial data on cardiac events and the understanding of the PK and PD of eplontersen, there is no scientific rationale to support the inclusion of 'Patients with NYHA functional classification ≥ 3' as Missing Information.

Overall, the incidence of cardiac Other Adverse Events of Interest (OAEIs) at Week 66 was much lower in the eplontersen group (13.9%) compared to the historical placebo (21.7%) or the historical inotersen group (22.3%). No individual cardiac disorder OAEIs was notably higher incidence in the eplontersen group compared to the external placebo or historical inotersen groups. Therefore, there is no rationale to suspect the safety profile in this population is different to that of the general target population.

Paediatric Population < 18 Years of Age

Reason for Exclusion:
Paediatric patients < 18 years of age were excluded from clinical studies as they are outside of the intended indication for eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:
Use of eplontersen in children and adolescents < 18 years of age is not indicated and therefore this population is not relevant for the proposed indication.

Geriatric Population > 82 Years of Age

Reason for Exclusion:
Patients > 82 years of age were excluded to avoid factors that may confound a complete understanding of the safety and efficacy data of eplontersen and to ensure interpretability of the data.

Is It Considered To Be Included as Missing Information: No

Rationale:
No overall differences in safety or effectiveness were observed between patients ≥65 years of age and younger adult patients, therefore no dose adjustment is required in elderly patients

(SmPC Section 4.2). There is no scientific rationale to suggest that the safety profile of eplontersen is affected by age.

Use in Patients with Low Platelet Count (History of Bleeding diathesis, or Coagulopathy [e.g., Liver Cirrhosis, Haematologic Malignancy, Antiphospholipid Antibody Syndrome, Congenital Disorders such as Haemophilia A, B, and Von Willebrand disease] or Platelets < 125 x 10^9/L)

Reason for Exclusion:
Inotersen is associated with reductions in PLT count, which may result in thrombocytopenia, as described in the SmPC.

Patients with a history of bleeding diathesis, coagulopathy, abnormal coagulation parameters, or low PLT values were excluded in the eplontersen clinical trials to avoid factors that may confound a complete understanding of the safety data of eplontersen and to ensure interpretability of the data.

Is It Considered To Be Included as Missing Information: No

Rationale:
Decreased PLT counts were observed in a subset of patients treated with eplontersen. These decreases were generally transient, did not lead to any bleeding events, and generally resolved while on continued treatment with eplontersen. Therefore, there is no scientific rationale to suspect that the safety profile in this patient population may differ to that characterised so far in the general target population.

Abnormal Thyroid Function Tests with Clinical Significance

Reason for Exclusion:
As TTR is a carrier protein for thyroxine and therefore could impact thyroxine levels, it was hypothesised that a reduction in plasma TTR protein may also result in decreased levels of total thyroxine. Patients with clinically significant abnormal thyroid stimulating hormone (TSH) values were excluded to allow for better interpretation of thyroid function data.

Is It Considered To Be Included as Missing Information: No

Rationale:
There were no adverse trends in TSH or free thyroxine in healthy volunteers and patients with ATTRv who received eplontersen during clinical studies. Therefore, there is no scientific rationale to suspect that the safety profile of eplontersen in this patient population may differ to that characterised so far in the general target population.

Karnofsky Performance Status ≤ 50%

Reason for Exclusion:
Patients with a Karnofsky performance status score of ≤ 50% were excluded to avoid factors that may confound a complete understanding of the efficacy data of eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:
There is no scientific rationale to suspect that the safety profile of eplontersen in this patient population may differ to that characterised so far in the general target population.

Prior or Anticipated Liver Transplant

Reason for Exclusion:
Patients with prior or anticipated liver transplant were excluded to avoid factors that may confound a complete understanding of the safety data of eplontersen and to ensure interpretability of the data.

Is It Considered To Be Included as Missing Information: No

Rationale:
It is expected that patients who have undergone a liver transplant may be exposed to eplontersen as it remains a treatment option in ATTRv patients. However, there is no scientific rationale to suspect that the safety profile in patients with prior or planned liver transplant will be different from that in the target population given the hepatic adverse event profile of eplontersen and due to its low immunogenicity and pro-inflammatory profile.

Up to Week 66, the incidence of abnormal liver function OAEI was similar between the eplontersen group (6.3%) and external placebo group (6.7%) and lower than historical inotersen group (12.5%). The proportion of patients was similar in the eplontersen group compared to the external placebo group for the following liver abnormalities: ALT ≥ 3 × ULN (0.7% versus 3.3%), AST ≥ 3 × ULN (0.7% versus 1.7%), and total bilirubin >2 × ULN (1.4% versus 1.7%).

Based on the comparisons made above along with the expected treatment progression, this population is not considered missing information.

Use in Patients with Renal Insufficiency as Defined by eGFR < 45 mL/min/1.73 m^2

Reason for Exclusion:
Patients with renal insufficiency as defined by eGFR < 45 mL/min/1.73 m^2 were originally excluded from clinical studies of eplontersen due to concerns raised with inotersen, which is associated with glomerulonephritis. As such, these patients were excluded to avoid factors that

may confound a complete understanding of the safety data of eplontersen and to ensure interpretability of the data.

Is It Considered To Be Included as Missing Information: No

Rationale:
Use in patients with < 45 mL/min/1.73 m^2 has not been studied. However, no dose adjustment is necessary in patients with mild to moderate renal impairment (estimated eGFR ≥ 45 to < 90 mL/min/1.73 m^2) (see Section 4.2 of SmPC).

There is no scientific rationale to suspect that the safety profile of eplontersen in this patient population may differ to that characterised so far in the general target population. The low observed 24-hour renal excretion fraction, the minor impact of renal impairment for other GalNAc-conjugated ASOs, and the lack of clinically meaningful differences found by the population PK and PKPD analysis support a limited impact of renal impairment on the PK or PD of eplontersen.

No safety concerns have been identified in the clinical studies to date relating to renal function, and thus future clinical studies with eplontersen will have an eGFR exclusion cut-off of < 30 mL/min/1.73 m^2. Glomerulonephritis has not been observed with eplontersen.

Use in Patients with Hepatic Impairment as Defined by ALT/AST > 2×ULN or Bilirubin ≥ 1.5×ULN

Reason for Exclusion:
Patients with hepatic impairment as defined by ALT/AST > 2×ULN or bilirubin ≥ 1.5×ULN were excluded as to not confound a complete understanding of the safety data of eplontersen and to ensure interpretability of the data.

Is It Considered To Be Included as Missing Information: No

Rationale:
Use in patients with moderate or severe hepatic impairment has not been studied. However, there are no dose adjustments necessary for patients with mild hepatic impairment (see Section 4.2 of SmPC). A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of eplontersen based on mild hepatic impairment (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST). Based on the knowledge of the pharmacokinetic profile of eplontersen there is no expectation that the safety profile would be different in those with moderate to severe hepatic impairment from those with mild hepatic impairment.

Active Infection Requiring Systemic Antiviral or Antimicrobial Therapy

Reason for Exclusion:
Patients with an active infection requiring systemic antiviral or antimicrobial therapy were excluded to avoid factors that may confound a complete understanding of the safety data of eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:
There is no scientific rationale to suspect that the safety profile in this patient population may differ to that characterised so far in the general target population.

Use in Patients With a Known History of or Positive Test for HIV, Hepatitis C, or Hepatitis B

Reason for Exclusion:
Patients with a known history of or a positive test for HIV, hepatitis C, or hepatitis B were excluded to avoid the potential confounding effect of the natural history of these conditions on a complete understanding of the safety data of eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:
The anticipated use in patients with ATTRv-PN and a known history of or positive test for HIV, hepatitis C, or hepatitis B is expected to be very low as this population is rare. This population is therefore not relevant for consideration as missing information.

Uncontrolled Hypertension (Blood Pressure > 160/100 mmHg)

Reason for Exclusion:
Patients with uncontrolled hypertension were excluded in order to avoid factors that may confound a complete understanding of the safety and efficacy data in the cardiac involvement subgroup analysis.

Is It Considered To Be Included as Missing Information: No

Rationale:
Analysis of data from ION-682884-CS3 did not reveal any signals for an adverse effect of eplontersen on blood pressure. Therefore, there is no scientific rationale to suspect that the safety profile of eplontersen in this patient population may differ to that characterised so far in the general target population.

Malignancy Within 5 Years, Except for Basal or Squamous Cell Carcinoma of the Skin, Melanoma in Situ, Prostate Carcinoma Grade Group 1, Breast Ductal Carcinoma in Situ, or Carcinoma in Situ of the Cervix. Patients With a History of Other Malignancies Who Have Been Treated With Curative Intent and Without Recurrence Within 5 Years

Reason for Exclusion:

Patients with malignancy within 5 years, except for those listed above, were excluded in order to avoid factors that may confound a complete understanding of the safety data of eplontersen and to ensure interpretability of the data.

Is It Considered To Be Included as Missing Information: No

Rationale:

There is no scientific rationale to suspect that the safety profile of eplontersen in this patient population may differ to that characterised so far in the general target population.

Use in Patients with Diabetes Mellitus or HbA1C > 7%

Reason for Exclusion:

Patients with diabetes mellitus or HbA1C > 7% were excluded to avoid factors (i.e., diabetic neuropathy) that may confound a complete understanding of the efficacy data of eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:

There is no scientific rationale to suspect that the safety profile of eplontersen in this patient population may differ to that characterised so far in the general target population.

Other Causes of Sensorimotor or Autonomic Neuropathy (e.g., Autoimmune Disease)

Reason for Exclusion:

Patients with other causes of sensorimotor or autonomic neuropathy were excluded to avoid factors that may confound a complete understanding of the efficacy data of eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:

There is no scientific rationale to suspect that the safety profile of eplontersen in this patient population may differ to that characterised so far in the general target population.

Known Immunoglobulin Light Chain Amyloidosis or Leptomeningeal Amyloidosis

Reason for Exclusion:

Patients with known immunoglobin light chain amyloidosis or leptomeningeal amyloidosis were excluded as they are outside of the intended indication for eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:
Use of eplontersen in patients with known immunoglobulin light chain amyloidosis or leptomeningeal amyloidosis is not expected as it is outside of the intended indication.

Monoclonal Gammopathy of Undetermined Significance and/or Alterations in Immunoglobulin Free Light Chain Ratio Unless Fat, Bone Marrow, or Heart Biopsy Confirms the Absence of Light Chain and the Presence of TTR Protein by Mass Spectrometry or Immunoelectron Microscopy

Reason for Exclusion:
Patients with known monoclonal gammopathy of undetermined significance and/or alterations in immunoglobulin free light chain ratio unless testing as noted above confirms the absence of light chain and presence of TTR protein were excluded as they are outside of the intended indication for eplontersen.

Is It Considered To Be Included as Missing Information: No

Rationale:
Use of eplontersen in patients with monoclonal gammopathy of undetermined significance and/or alterations in immunoglobulin free light chain ratio unless testing as noted above confirms the absence of light chain and presence of TTR protein is not expected as it is outside of the intended indication.

II.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme focuses on a rare disease indication and is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

II.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table II-7 Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure [Number of patients][a]
Pregnant women	Not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic impairment *(ALT or AST > 3×ULN and/or bilirubin > 1.5×ULN)*	• 2 (1.2%)[b]

Table II-7 Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure [Number of patients][a]
Patients with renal impairment *(eGFR < 45 mL/min/1.73 m^2)*	• 1 (0.6%)
Patients with a disease severity different from inclusion criteria in clinical trials • (NIS > 130 or NIS < 10)	• 5 (1.2%)
Patients with cardiovascular impairment *(NYHA classification)* • NYHA Class I • NYHA Class II • NYHA Class ≥ 3	• 119 (71.3%)[c] • 45 (26.9%)[c] • 0
Immunocompromised patients	Exposure data for this population are not available.
Patients with relevant different ethnic origin • Not Hispanic or Latino • Hispanic or Latino	• N=139 (84.2%)[d] • N= 26 (15.8%) [d]
Subpopulations carrying relevant genetic polymorphisms: • Detectable Val30MetTTRmutation • Non-Val30Met TTR mutation	• N=98 (58.7%) • N=69 (41.3%)

[a] Includes all available data in Eplontersen Treated set (N=167).

[b] One patient experienced an ALT >3xULN prior to the first dose of eplontersen. There were no patients with ALT/ AST > 3xULN at study baseline.

[c] Data on NYHA classification was missing for 3 (1.8%) patients.

[d] Ethnicity data were missing for 2 patients in the Eplontersen Treated set. Reported exposure from the remaining 165 of total 167 patients.

II.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

II.5.1 Method used to calculate exposure

Not applicable.

II.5.2 Exposure

Not applicable.

II.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for Misuse for Illegal Purposes

Eplontersen does not cross the blood-brain barrier and has no known effects on the central nervous system. There is currently no evidence of any potential for misuse of eplontersen for illegal purposes.

II.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

II.7.1 Identification of safety concerns in the initial RMP submission

II.7.1.1 Risk not considered important for inclusion in the list of safety concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the initial (version 1) EU RMP which will not be updated.

2.7.1.1.1 Known risks that do not impact the benefit-risk profile:

- Injection site reactions

Injection site reactions (including injection site erythema, injection site pain, and injection site pruritis) were commonly observed in eplontersen-treated groups. These events were however self-limiting or could be managed using symptomatic over-the-counter treatment. These reactions are managed according to standard clinical practice and product labelling (see Section 4.8 of the SmPC)

- Vomiting

Vomiting was a commonly observed event in eplontersen-treated groups. This event can be managed using symptomatic treatment or according to standard clinical practice and product labelling (see Section 4.8 of the SmPC).

2.7.1.1.2 Other reasons for not considering risks important:

- Hypersensitivity

The incidence of TEAEs of hypersensitivity (search via MedDRA Hypersensitivity SMQ [narrow and broad version]) was lower in the Up to Week 66 Eplontersen group (18.8%) compared to the external placebo group (26.7%). The most reported TEAEs of

hypersensitivity were in the skin and subcutaneous tissue disorders SOC with similar incidence between the Eplontersen group and the external placebo group (11.8% vs 11.7%). Most of these patients had a past medical history of hypersensitivity to other drugs or skin-related disorders. Most of the events were mild or moderate in severity, none were severe or serious, and most were reported as not related to the study drug by the Investigator. None of the skin related TEAEs led to discontinuation of study drug and most of the events resolved without any treatment.

In the Eplontersen Treated Set (as of 07 April 2023), most of the TEAEs were mild to moderate in severity and were assessed as not related to the study drug by the Investigator. Two serious and severe TEAEs (PTs: respiratory failure and shock) were reported in one patient. The serious and the severe TEAEs resolved while on eplontersen treatment and were not assessed as related to the study drug by the Investigator. None of the TEAEs led to interruption or discontinuation of the study drug. No TEAEs of anaphylaxis were reported in the eplontersen clinical programme.

Overall, the data suggest that TEAEs of hypersensitivity were not associated with eplontersen treatment. Hypersensitivity is not considered an identified or potential risk, nor does it impact the benefit-risk profile of eplontersen. There are no additional risk minimisation measures or additional pharmacovigilance activities required and hypersensitivity is not considered a safety concern for eplontersen.

II.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The following topics were classified as important risks in the initial (Version 1) EU RMP and will not be updated:

Important Identified Risks

There are no identified risks considered important for eplontersen.

Important Potential Risk - Ocular Adverse Events due to Vitamin A Deficiency

Risk-benefit Impact:

Eplontersen is an ASO drug targeted to human TTR gene mRNA. Hybridisation to the cognate TTR gene mRNA results in the ribonuclease H1-mediated degradation of the mRNA, inhibiting production of the TTR protein. A known function of TTR in the plasma is to transport retinol (vitamin A) to tissues through its association with RBP4. The retinol-RBP4 complex in turn binds to TTR, which prevents the complex from being excreted through the kidney. Other mechanisms also exist for vitamin A transport to tissues. A decrease in serum concentration of vitamin A is therefore an expected consequence of the mechanism of action of eplontersen.

Clinical consequences of vitamin A deficiency, including ocular AEs, are included in the list of safety concerns for the TTR silencers inotersen, patisiran, and vutrisiran.

In the Eplontersen Treated Set, 87.2 % of patients who had normal vitamin A levels at baseline had low vitamin A levels during treatment. Mean vitamin A values decreased in the eplontersen group and remained lower throughout the study compared with the external placebo group. A higher incidence of vitamin A values below the lower limit of normal at any time post-baseline was observed in the Up to Week 66 Eplontersen group (95.1%) compared with the external placebo group (3.3%). Similarly, an incidence of vitamin A values below the lower limit of normal at any time post-baseline was observed at 95.1% in the Eplontersen Treated Set up to data cut-off of 07 April 2023.

Missing Information – Use in pregnant women and effects on pregnancy outcomes

Risk-benefit Impact:

Patients who are pregnant and/or lactating were excluded from participating in clinical trials in order to avoid potential harm to the unborn foetus or breastfed infant. Women of childbearing potential were required to use highly effective contraceptive methods and negative pregnancy tests were required during screening and prior to dosing of eplontersen. There are therefore no data on use of eplontersen during pregnancy and lactation.

The age of disease onset for ATTRv-PN is between 30 and 50 years for those with the V30M TTR mutation. Woman of childbearing potential are therefore among the target population for treatment with eplontersen. Additionally, maternal vitamin A levels above or below the normal range may be associated with an increased risk of foetal malformation. It is not known whether vitamin A supplementation would be sufficient to reduce the risk to the foetus. For these reasons, use in pregnant women and effects on pregnancy outcomes is considered to be missing information and further information is required on the safety profile of eplontersen in this population.

II.7.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

II.7.3 Details of important identified risks, important potential risks, and missing information

II.7.3.1 Presentation of important identified risks and important potential risks

Important Potential Risk: Ocular Adverse Events Due to Vitamin A Deficiency

Potential Mechanisms:

Eplontersen inhibits production of the TTR protein. A known function of TTR in the plasma is to transport retinol (vitamin A) to tissues through its association with RBP4. The retinol-RBP4 complex binds to TTR, which prevents the complex from being excreted through the kidney. Other mechanisms also exist for vitamin A transport to tissues. A decrease

in serum concentration of vitamin A is therefore an expected consequence of the mechanism of action of eplontersen.

Evidence Source(s) and Strength of Evidence:

The assessment of ocular AEs potentially due to vitamin A deficiency was conducted through a non-specific, concatenated MedDRA search that included a predefined set of PTs for either vitamin A deficiency or ocular AEs. This search strategy was used as a screening tool for potential events and is non-specific, so none of the events identified were definitively ocular AEs specifically related to vitamin A deficiency. Based on the search strategy, the incidence of ocular AEs potentially related to vitamin A deficiency (AESIs) was 27.1 % (n = 39) in the Up to Week 66 Eplontersen group compared with 15.0 % (n = 9) in the external placebo group. Main contributors to the imbalance were vitamin A deficiency and vitamin A decreased. It should be noted that vitamin A laboratory values were available to the Investigator in the eplontersen group in Study ION-683844-CS3 while they were blinded to the investigator during ISIS 420915-CS2 (External Placebo). Hence no TEAEs of vitamin A decreased or vitamin A deficiency were reported in the external placebo group. Excluding these two PTs, the incidence of ocular AESIs was similar between the Up to Week 66 Eplontersen group (16.7 % [n=24])) and the external placebo group (15.0 % [n=9]).

Table II-8 Characterisation of Ocular Adverse Events Potentially Related to Vitamin A Deficiency

		Up to Week 66[a]						On Study	
		ISIS 420915-CS2				ION-682884-CS3		Pooled	
		Placebo[b] (N=60)		Inotersen[b] (N=112)		Eplontersen 45 mg q4wk[c] (N=144)		Eplontersen Treated Set[d] (N=167)	
		Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events	Patients n (%)	Events
Frequency	Any AE	9 (15.0)	10	21 (18.8)	23	39 (27.1)	55	48 (28.7)	66
	SAE	0	0	0	0	0	0	1 (0.6)	1
Intensity	Mild	9 (15.0)	10	20 (17.9)	21	32 (22.2)	44	37 (22.2)	51
	Moderate	0	0	2 (1.8)	2	10 (6.9)	11	13 (7.8)	14
	Severe	0	0	0	0	0	0	1 (0.6)	1
Outcome	Recovered/ resolved	2 (3.3)	2	6 (5.4)	7	16 (11.1)	18	22 (13.2)	24
	Not recovered/ not resolved	8 (13.3)	8	16 (14.3)	16	29 (20.1)	37	32 (19.2)	42
	Death	0	0	0	0	0	0	0	0
Action for adverse event	Dose not changed	9 (15.0)	10	21 (18.8)	23	39 (27.1)	55	48 (28.7)	66

[a] Up to Week 66: Time from first dose up to study day 456, up to data cut-off, or up to last contact, whichever comes first.

[b] Placebo and inotersen arms were drawn from ISIS 420915-CS2. All data collected from the first dose of investigational product in ISIS 420915-CS2 up to study day 456 were included.

[c] Includes all patients who received eplontersen from the beginning of ION-682884-CS3. All data collected from the first dose of eplontersen q4wk in ION-682884-CS3 up to study day 456 were included. Here, 'Eplontersen 45 mg q4wk' includes patients in the ION-682884-CS3 arm 'Eplontersen 45 mg q4wk' ('non-switchers') only;
all other ION-682884-CS3 patients are excluded, particularly those in the 'Inotersen 300 mg q1w/Eplontersen 45 mg q4wk' arm ('switchers').

[d] Eplontersen Treated Set: Includes all patients who received at least 1 dose of eplontersen in the ION-682884-CS3 or ION-682884-C13 study.

[redacted]

Risk Factors and Risk Groups

Patients with a clinical history of vitamin A deficiency.

Preventability

Patients receiving eplontersen should take oral supplementation of the daily recommended dose of vitamin A to reduce the potential risk of ocular AEs due to vitamin A deficiency (see Section 4.4 of SmPC). Referral for ophthalmological assessment is recommended if patients develop ocular symptoms consistent with vitamin A deficiency.

Impact on the Risk-benefit Balance of the Product:

Clinical consequences of vitamin A deficiency can include ocular AEs such as reduced night vision or night blindness and persistent dry eyes.

Public Health Impact

As the impact is to the treated population only, there is no public health impact.

II.7.3.2 Presentation of missing information

Missing Information: Use in pregnant women and effects on pregnancy outcomes

Evidence Source:

Patients who are pregnant and/or lactating were excluded from participating in clinical trials in order to avoid potential harm to the unborn foetus or breastfed infant. Women of childbearing potential were required to use highly effective contraceptive methods and negative pregnancy tests were required during screening and prior to dosing of eplontersen. There are therefore no data on use of eplontersen during pregnancy and lactation.

The age of disease onset for ATTRv-PN is between 30 and 50 years for those with the V30M TTR mutation. Woman of childbearing potential are therefore among the target population for treatment with eplontersen. Additionally, maternal vitamin A levels above or below the normal range may be associated with an increased risk of foetal malformation. It is not known whether vitamin A supplementation would be sufficient to reduce the risk to the foetus. For these reasons, use in pregnant women and effects on pregnancy outcomes is considered to be missing information and further information is required on the safety profile of eplontersen in this population.

Population in Need of Further Characterization:

Use of eplontersen in pregnant women will be evaluated to determine the effect, if any, on the outcome of pregnancy and foetus. The evaluation will be made through routine pharmacovigilance activities.

II.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

II.8.1 Summary of the safety concerns

Table II-9 Summary of Safety Concerns

Important identified risks	• None
Important potential risks	• Ocular adverse events due to vitamin A deficiency
Missing information	• Use in pregnant women and effects on pregnancy outcomes

III. PART III: PHARMACOVIGILANCE PLAN

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for ocular adverse events due to vitamin A deficiency.

A structured targeted questionnaire will be used to obtain further information regarding reported suspected adverse reactions of ocular adverse events due to vitamin A deficiency. The questionnaire has been designed to collect information pertaining to the clinical course of the event, the signs and symptoms observed, eplontersen treatment received, relevant medical history, concomitant medications, risk factors, treatment received for the event, relevant laboratory results and other signs and symptoms of Vitamin A deficiency. The targeted questionnaire is provided in Annex 4 of this RMP.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

ION-682884-CS13: An Open-Label, Extension Study to Assess the Long-Term Safety and Efficacy of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Study short name and title:
Study to Assess the Long-Term Safety and Efficacy of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Rationale and Objectives:
The primary objective is to evaluate the long-term safety and tolerability of extended dosing with ION-682884 (eplontersen) in patients with hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN).

Study Design:
Phase III, Open-Label Study

Milestones:
Final Clinical Study Report (CSR) Submission: Q3 2027

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table III-1 Summary of Additional Pharmacovigilance Activities for eplontersen in GB

Study # Study Name	Summary of Objective	Safety Concern	Milestone	Due Date
Category 3 PASS Study				
Study ION-682884-CS13 (Ongoing)	To evaluate the safety and tolerability of extended dosing with ION-682884 in patients with hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN).	• Ocular adverse events due to vitamin A deficiency	Final CSR submission	Q3 2027

IV. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

V. PART V: RISK MINIMISATION MEASURES

V.1 ROUTINE RISK MINIMISATION MEASURES

Table V-1 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Ocular adverse events due to vitamin A deficiency	Routine risk communication: • SmPC Section 4.4 • PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance on the investigation of signs and symptoms of vitamin A deficiency and the need for evaluation of ocular signs or symptoms of vitamin A deficiency prior to initiation of eplontersen treatment in SmPC Section 4.4 and PIL Section 2 • Recommendation for oral supplementation of vitamin A in SmPC Section 4.4 and PIL Section 2 • Guidance on the ocular symptoms that should trigger an ophthalmology referral in SmPC Section 4.4 Other routine risk minimisation measures beyond the Product Information: • Legal status (prescription only medication)
Use in pregnant women and effects on pregnancy outcomes	Routine risk communication: • SmPC Sections 4.4 and 4.6 • PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Recommendation that pregnancy should be excluded prior to initiation of treatment, that women of childbearing potential should practice effective contraception during treatment, and details of actions that should be taken should a woman intend to become pregnant or should an unplanned pregnancy occur during eplontersen treatment in SmPC Section 4.6 and PIL Section 2 Other routine risk minimisation measures beyond the Product Information: • Legal status (prescription only medication)

V.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMISATION MEASURES

Table V-2 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Ocular adverse events due to vitamin A deficiency	Routine risk minimisation measures: • SmPC Section 4.4 (including vitamin A supplementation) • PIL Section 2 (including vitamin A supplementation) • Legal status (prescription only medication) Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Structured targeted questionnaire Additional pharmacovigilance activities: • Study ION-682884-CS13 (Category 3 PASS)
Use in pregnant women and effects on pregnancy outcomes	Routine risk minimisation measures: • SmPC Sections 4.4 and 4.6 • PIL Section 2 • Recommendation that pregnancy should be excluded prior to initiation of treatment, that women of childbearing potential should practice effective contraception during treatment, and details of actions that should be taken should a woman intend to become pregnant or should an unplanned pregnancy occur during eplontersen treatment in SmPC Section 4.6 and PIL Section 2 • Legal status (prescription only medication) Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

VI. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR WAINZUA (EPLONTERSEN)

This is a summary of the risk management plan (RMP) for Wainzua. The RMP details important risks of Wainzua, how these risks can be minimised, and how more information will be obtained about Wainzua's risks and uncertainties (missing information).

Wainzua's SmPC and its package leaflet (PIL) give essential information to healthcare professionals and patients on how Wainzua should be used.

This summary of the RMP for Wainzua should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Wainzua's RMP.

VI.1 THE MEDICINE AND WHAT IT IS USED FOR

Wainzua is authorised for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (see SmPC for the full indication). It contains eplontersen as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Wainzua's benefits can be found in Wainzua's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage **<** link to the EPAR summary landing page>**.**

VI.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Wainzua, together with measures to minimise such risks and the proposed studies for learning more about Wainzua's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Wainzua is not yet available, it is listed under 'missing information' below.

VI.2.1 List of important risks and missing information

Important risks of Wainzua are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Wainzua. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table VI-1 List of Important Risks and Missing Information

Important identified risks	• None
Important potential risks	• Ocular adverse events due to vitamin A deficiency
Missing Information	• Use in pregnant women and effects on pregnancy outcomes

VI.2.2 Summary of important risks

Table VI-2 Important Potential risk- Ocular Adverse Events Due to Vitamin A Deficiency

Evidence for linking the risk to the medicine	The assessment of ocular adverse events due to vitamin A deficiency was conducted through a non-specific, concatenated MedDRA search that included a predefined set of PTs for either vitamin A deficiency or ocular adverse events. This search strategy was used as a screening tool for potential events and is non-specific, so none of the events identified were definitively ocular adverse events specifically related to vitamin A deficiency. Based on the search strategy, the incidence of ocular adverse events potentially related to vitamin A deficiency (adverse events of special interest) was 27.1% (n = 39) in the Up to Week 66 Eplontersen group compared with 15.0% (n = 9) in the external placebo group. Main contributors to the imbalance were vitamin A deficiency and vitamin A decreased. It should be noted that vitamin A laboratory values were available to the Investigator in the eplontersen group in Study ION-683844-CS3 while they were blinded to the investigator during ISIS 420915-CS2 (External Placebo). Hence no TEAEs of vitamin A decreased or vitamin A deficiency were reported in the external placebo group. Excluding these two PTs, the incidence of ocular AESIs was similar between the Up to Week 66 Eplontersen group (16.7 % [n=24])) and the external placebo group (15.0 % [n=9]).
Risk factors and risk groups	Patients with a clinical history of vitamin A deficiency.
Risk minimisation measures	Routine risk minimisation measures • SmPC Section 4.4 • PIL Section 2 • Guidance on the investigation of signs and symptoms of vitamin A deficiency and the need for evaluation of ocular signs or symptoms of vitamin A deficiency prior to initiation of eplontersen treatment in SmPC Section 4.4 and PIL Section 2 • Recommendation for oral supplementation of vitamin A in SmPC Section 4.4 and PIL Section 2 • Guidance on the ocular symptoms that should trigger an ophthalmology referral in SmPC Section 4.4 • Legal status (prescription only medication) Additional risk minimisation measures • None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Study ION-682884-CS13 (Category 3 PASS)

Table VI-3 Missing Information – Use in Pregnant women and effects on pregnancy outcomes

Risk minimization measures	Routine risk minimization measures • SmPC Sections 4.4 and 4.6 • PIL Section 2 • Recommendation that pregnancy should be excluded prior to initiation of treatment, that women of childbearing potential should practice effective contraception during treatment, and details of actions that should be taken should a woman intend to become pregnant or should an unplanned pregnancy occur during eplontersen treatment in SmPC Section 4.6 and PIL Section 2 • Legal status (prescription only medication) Additional risk minimization measures • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • None

VI.2.3 Post-authorisation development plan

VI.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Wainzua.

VI.2.3.2 Other studies in post-authorisation development plan

Category 3 PASS

ION-682884-CS13

Study short name and title:

Study to Assess the Long-Term Safety and Efficacy of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Rationale and Objectives:

The primary objective is to evaluate the long-term safety and tolerability of extended dosing with ION-682884 (eplontersen) in patients with hereditary transthyretin-mediated amyloid polyneuropathy (hATTR-PN).

VII.4 ANNEX 4: SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

AstraZeneca

OCULAR EVENT QUESTIONNAIRE

AZ CASE ID #

Reporter's Information		
Reporter's Name:	Is Reporter a healthcare professional? ☐ No ☐ Yes, if yes, please provide specialty:	Telephone #:
Reporter's Address: Country:	Reporter's Signature:	Date *(DD/MM/YY)*:

1. Patient's Details		
Initials:	Gender at birth: ☐ Male ☐ Female For female, currently or recently pregnant? ☐ No ☐ Yes	Date of Birth *(DD/MM/YYYY)*: Age *(years)*: Height: ____ cm in Weight: ____ kg lb

Race: ☐ White ☐ Black or African American ☐ Native Alaska or American Indian ☐ Asian ☐ Refused or Unknown

Ethnic Group: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Refused or Unknown

2. ADVERSE EVENT(S)

1. Ocular event(s) details:
   - When was the ocular event(s) detected?
     _____
   - Was the patient seen by an ophthalmologist (yes/no)? If yes, please provide the details of the ocular examination.
     _____
   - Was treatment initiated for the patient's ocular event? If yes, provide details in Section 4
   - Is the event(s) causally related to eplontersen (yes/no)? If yes, please provide details.
     _____
   - What was the outcome of the ocular event(s)? If resolved, please provide the end date.
     _____
   - Any previous episodes of ocular event(s) during eplontersen treatment? If yes, provide details:
     _____

AstraZeneca

OCULAR EVENT QUESTIONNAIRE V1.0

AZ CASE ID # **JANUARY 08 2024**

- What was the Vitamin A dosing (Start/stop dates, dose and frequency, etc.):

_____

Was the patient hospitalized for the ocular event(s)? ☐ No ☐ Yes

2. Did the patient have any of the following ocular symptoms or signs? If yes, please provide the date of onset and all clinical details for each of the observed symptoms or signs in the narrative field on page 3.

- Difficulty to see in dark environment or reduced night vision Yes No
- Difficulty in dark adaptation Yes No
- Dry eye symptoms:
  - ❖ Discomfort: Scratchy, gritty, sandy, burning or stinging sensation of the eyes Yes No
  - ❖ Discomfort in bright light or photophobia Yes No
  - ❖ Mucus discharge Yes No
  - ❖ Watery eyes or excessive tearing Yes No
- Signs on slit lamp examination:
- Conjunctival dryness/xerosis with or without Bitot's spot Yes No
- Cornea:
  - ❖ Corneal xerosis, punctate epithelial erosion, keratinization Yes No
  - ❖ Corneal ulceration/scar Yes No
  - ❖ Corneal melting Yes No
  - ❖ Corneal perforation Yes No
- Fundoscopy: Retinopathy

Other signs or symptoms:

- Dry or scaly skin Yes No
- Phrynorderma ("toad skin") Yes No
- Pruritus Yes No
- Hyperkeratosis Yes No
- Easily broken finger nails Yes No
- Erythema Yes No
- Dry lips and thickened tongue Yes No

3. EPLONTERSEN TREATMENT

1. What was the start date of eplontersen treatment?
2. Has eplontersen treatment been discontinued? If yes, date of discontinuation (*DD/MM/YY*): _____
3. Was there any change in eplontersen treatment as a result of the ocular event(s) (dose frequency change, dose pause, etc.)? _____ If yes, what was the treatment change and dates?
4. What dose/frequency of eplontersen was the patient receiving at the time of detection of ocular event(s)?

_____

4. How was the patient treated?

AstraZeneca

OCULAR EVENT QUESTIONNAIRE V1.0

AZ CASE ID # **JANUARY 08 2024**

Was treatment provided? ☐ No ☐ Yes

If yes, please provide the details of treatment (start date, stop date, dose, and frequency etc.):

Please describe medication or other treatments and the treatment outcome(s).

Other treatments - please specify:

5. Other Suspect Drugs?

(Please only include other drugs you consider to be causally related to the adverse event(s) and not concomitant medications)

Suspect Drug Name	Indication	Dose and frequency	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was the suspect drug withdrawn?
						☐ No ☐ Yes
						☐ No ☐ Yes
						☐ No ☐ Yes

If any of the above drugs were stopped, did the event(s) improve after stopping?

☐ No ☐ Yes ☐ Not applicable

If applicable, please provide Date Drug was Stopped/Altered *(DD/MM/YY)*: _____

Did the event(s) reoccur after reintroduction?

☐ No ☐ Yes ☐ Not applicable

If applicable, please provide Date Drug was Reintroduced *(DD/MM/YY)*: _____

6. Concomitant Medications

(Please exclude drugs used to treat the event(s). List all medications taken by the patient, including over-the-counter drugs, supplements, and herbal preparations)

Drug Name	Indication	Dose and frequency	Route	Start Date *(DD/MM/YY)*	Stop Date *(DD/MM/YY)*	Was concomitant medication withdrawn?
						☐ No ☐ Yes

AstraZeneca

OCULAR EVENT QUESTIONNAIRE V1.0

AZ CASE ID # **JANUARY 08 2024**

						☐ No ☐ Yes
						☐ No ☐ Yes

7. Relevant Medical History/ Concurrent Diseases

Please provide dates of onset or diagnosis and clinical details whenever possible for any item below:

Does the patient have a past history or current diagnosis of any of the following conditions?

Previous episode of vitamin A deficiency _____

Alcoholism _____

Fat malabsorption _____

Pancreatic insufficiency _____

Inflammatory bowel disease _____

Crohn's disease _____

Small bowel bypass surgery _____

Pancreatitis _____

Biliary obstruction _____

Liver disease (e.g. cirrhosis) _____

Other condition leading to malabsorption: _____

Other vitamin or mineral deficiency: _____

Other:

1. Ocular history:

   _____

2. In Section 6 (Concomitant Medications), please list all medications taken by the patient, including over the counter drugs or herbal preparations. Please provide details of start dates, indications for use, and recent dosage changes. Additionally, please confirm if the patient has taken the following medications. If yes, please provide details in Section 6:

   Cholestyramine..... Yes No
   Mineral oil ..... Yes No

AstraZeneca

OCULAR EVENT QUESTIONNAIRE V1.0

AZ CASE ID # **JANUARY 08 2024**

8. Relevant Laboratory Results-in relation to the ocular event(s). Please provide and attach results of any relevant laboratory and diagnostic procedures performed, if available
9. ADVERSE EVENT(S) NARRATIVE

Thank you for completing this form.

VII.6 ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES – NOT APPLICABLE

VIII. LIST OF REFERENCES

Aimo et al 2021
Aimo A, Rapezzi C, Perfetto F, Cappelli F, Palladini G, Obici L, et al. Quality of life assessments in amyloid transthyretin (ATTR) amyloidosis. Eur J Clin Invest. 2021;51(11):e13598.

American Heart Association 2022
American Heart Association. What is hATTR amyloidosis? [Internet], c2022. [cited 2023 Sep 19]. Available from: https://www.heart.org/-/media/Files/Health-Topics/Answers-by-Heart/What-is-hATTR-Amyloidosis.pdf.

Ando et al 2013
Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31.

Andreou et al 2018
Andreou S, Panayiotou E, Michailidou K, Pirpa P, Hadjisavvas A, El Salloukh A, et al. Epidemiology of ATTRV30M neuropathy in Cyprus and the modifier effect of complement C1q on the age of disease onset. Amyloid. 2018;25(4):220-6.

Auer-Grumbach et al 2020
Auer-Grumbach M, Rettl R, Ablasser K, Agis H, Beetz C, Duca F, et al. Hereditary ATTR amyloidosis in Austria: prevalence and epidemiological hot spots. J Clin Med. 2020;9(7):2234.

Barreiros et al 2013
Barreiros AP, Galle PR, Otto G. Familial amyloid polyneuropathy. Dig Dis. 2013;31(1):170-4.

Bourque et al 2016
Bourque PR, Shafi S, Jansen GH, McCurdy A, Chardon JW. Amyloid neuropathy following domino liver transplantation: response to diflunisal. JAMA Neurol. 2016;73(4):477-8.

Buades-Reinés et al 2016
Buades-Reinés J, Raya-Cruz M, Gallego-Lezaún C, Ripoll-Vera T, Usón-Martín M, Andreu-Serra H, et al. Transthyretin familial amyloid polyneuropathy (TTR-FAP) in Mallorca: a comparison between late- and early-onset disease. J Peripher Nerv Syst. 2016;21(4):352-6.

Butler et al 1997
Butler M, Stecker K, Bennett CF. Cellular distribution of phosphorothioate oligodeoxynucleotides in normal rodent tissues. Lab Invest. 1997;77(4):379-88.

Coelho et al 2013
Coelho T, Maurer MS, Suhr OB. THAOS - The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin. 2013;29(1):63-76.

Coelho et al 2018
Coelho T, Ericzon BG, Falk R, Grogan D, et al. A guide to transthyretin amyloidosis. Amyloidosis Foundation [Internet], c2018 [cited 2023 Sep 19]. Available from: https://amyloidosis.org/sites/default/files/pdf-docs/pages/resources/2023-03/2018%20ATTR.pdf.

EMA 2022
European Medicines Agency. Assessment report for Amvuttra (vutrisiran) [Internet], c2022. [cited 2023 Sep 19]. Available from: https://www.ema.europa.eu/en/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf.

Farman and Kornbrust 2003
Farman CA, Kornbrust DJ. Oligodeoxynucleotide studies in primates: antisense and immune stimulatory indications. Toxicol Pathol. 2003;31 Suppl:119-22.

Ferraro et al 2021
Ferraro PM, D'Ambrosio V, Di Paolantonio A, Guglielmino V, Calabresi P, Sabatelli M, et al. Renal involvement in hereditary transthyretin amyloidosis: an Italian single-centre experience. Brain Sci. 2021;11(8):980.

Galant et al 2017
Galant NJ, Westermark P, Higaki JN, Chakrabartty A. Transthyretin amyloidosis: an under-recognized neuropathy and cardiomyopathy. Clin Sci (Lond). 2017;131(5):395-409.

Gertz 2017
Gertz MA. Hereditary ATTR amyloidosis: burden of illness and diagnostic challenges. Am J Manag Care. 2017;23(7 Suppl):S107-S112.

Hawkins et al 2015
Hawkins PN, Ando Y, Dispenzeri A, Gonzalez-Duarte A, Adams D, Suhr OB. Evolving landscape in the management of transthyretin amyloidosis. Ann Med. 2015;47(8):625-38.

Hemming et al 1998
Hemming AW, Cattral MS, Chari RS, Greig PD, Lilly LB, Ashby P, et al. Domino liver transplantation for familial amyloid polyneuropathy. Liver Transpl Surg. 1998;4(3):236-8.

Henry et al 1997
Henry SP, Giclas PC, Leeds J, Pangburn M, Auletta C, Levin AA, et al. Activation of the alternative pathway of complement by a phosphorothioate oligonucleotide: potential mechanism of action. J Pharmacol Exp Ther. 1997;281(2):810-6.

Henry et al 2008
Henry SP, Kim T-W, Kramer-Stickland K, Zanardi TA, Fey RA, Levin AA. Toxicologic properties of 2'-O-methoxyethyl chimeric antisense inhibitors in animals and man. In: Crooke ST (ed.), Antisense drug technology: principles, strategies, and applications. Boca Raton, FL: CRC Press; 2008.

Holmgren et al 1994
Holmgren G, Costa PM, Andersson C, Asplund K, Steen L, Beckman L, et al. Geographical distribution of TTR met30 carriers in northern Sweden: discrepancy between carrier frequency and prevalence rate. J Med Genet. 1994;31(5):351-4.

Hund 2012
Hund E. Familial amyloidotic polyneuropathy: current and emerging treatment options for transthyretin-mediated amyloidosis. Appl Clin Genet. 2012;5:37-41.

Inês et al 2018
Inês M, Coelho T, Conceição I, Duarte-Ramos F, de Carvalho M, Costa J. Epidemiology of transthyretin familial amyloid polyneuropathy in Portugal: a nationwide study. Neuroepidemiology. 2018;51(3-4):177-82.

Koutsis et al 2021
Koutsis G, Kastritis E, Kontogeorgiou Z, Kartanou C, Kokotis P, Rentzos M, et al. Variant transthyretin amyloidosis (ATTRv) polyneuropathy in Greece: a broad overview with a focus on non-endemic unexplored regions of the country. Neuromuscul Disord. 2021;31(12):1251-8.

Lindmark et al 2021
Lindmark K, Pilebro B, Sundström T, Lindqvist P. Prevalence of wild type transtyrethin cardiac amyloidosis in a heart failure clinic. ESC Heart Fail. 2021;8(1):745-9.

Luigetti et al 2020
Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. Ther Clin Risk Manag. 2020;16:109-23.

Luigetti et al 2021
Luigetti M, Guglielmino V, Antonini G, Casali C, Ceccanti M, Chiappini MG, et al. ATTRv in Lazio-Italy: a high-prevalence region in a non-endemic country. Genes (Basel). 2021;12(6):829.

Mazzeo et al 2015
Mazzeo A, Russo M, Di Bella G, Minutoli F, Stancanelli C, Gentile L, et al. Transthyretin-related familial amyloid polyneuropathy (TTR-FAP): a single-center experience in Sicily, an Italian endemic area. J Neuromuscul Dis. 2015;2(s2):S39-S48.

Mejia Baranda et al 2022
Mejia Baranda J, Ljungberg J, Wixner J, Anan I, Oskarsson V. Epidemiology of hereditary transthyretin amyloidosis in the northernmost region of Sweden: a retrospective cohort study. Amyloid. 2022;29(2):120-7.

Parman et al 2016
Parman Y, Adams D, Obici L, Galán L, Guergueltcheva V, Suhr OB, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Current Opin Neurol. 2016;29 Suppl 1(Suppl 1):S3-13.

Planté-Bordeneuve et al 2007
Planté-Bordeneuve V, Ferreira A, Lalu T, Zaros C, Lacroix C, Adams D, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). Neurology. 2007;69(7):693-8.

Planté-Bordeneuve and Said 2011
Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. Lancet Neurol. 2011;10(12):1086-97.

Pozsonyi et al 2021
Pozsonyi Z, Peskó G, Takács H, Csuka D, Nagy V, Szilágyi A, et al. Variant transthyretin amyloidosis ATTRv in Hungary: first data on epidemiology and clinical features. Genes. 2021;12(8):1152.

Reinés et al 2014
Reinés JB, Vera TR, Martín MU, Serra HA, Campins MM, Millán JM, et al. Epidemiology of transthyretin-associated familial amyloid polyneuropathy in the Majorcan area: Son Llàtzer Hospital descriptive study. Orphanet J Rare Dis. 2014;9:29.

Russo et al 2020
Russo M, Obici L, Bartolomei I, Cappelli F, Luigetti M, Fenu S, et al. ATTRv amyloidosis Italian Registry: clinical and epidemiological data. Amyloid. 2020;27(4):259-65.

Samuelsson et al 2022
Samuelsson K, Jovanovic A, Egervall K, Anan I, Wixner J, Press R. Hereditary transthyretin amyloidosis in Sweden: comparisons between a non-endemic and an endemic region. Amyloid. 2022;29(4):220-7.

Schmidt et al 2018
Schmidt HH, Waddington-Cruz M, Botteman MF, Carter JA, Chopra AS, Hopps M, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. Muscle Nerve. 2018;57(5):829-37.

Sekijima 2015
Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry. 2015;86(9):1036-43.

Skrahina et al 2021
Skrahina V, Grittner U, Beetz C, Skripuletz T, Juenemann M, Krämer HH, et al. Hereditary transthyretin-related amyloidosis is frequent in polyneuropathy and cardiomyopathy of no obvious aetiology. Ann Med. 2021;53(1):1787-96.

Sousa et al 1993
Sousa A, Andersson R, Drugge U, Holmgren G, Sandgren O. Familial amyloidotic polyneuropathy in Sweden: geographical distribution, age of onset, and prevalence. Hum Hered. 1993;43(5):288-94.

Suhr et al 2016
Suhr OB, Larsson M, Ericzon BG, Wilczek HE. Survival after transplantation in patients with mutations other than Val30Met: extracts from the FAP World Transplant Registry. Transplantation. 2016;100(2):373-81.

Thenappan et al 2014
Thenappan T, Fedson S, Rich J, Murks C, Husain A, Pogoriler J, Anderson AS. Isolated heart transplantation for familial transthyretin (TTR) V122I cardiac amyloidosis. Amyloid. 2014;21(2):120-3.

Tzagournissakis et al 2022
Tzagournissakis M, Foukarakis E, Samonakis D, Tsilimbaris M, Michaelidou K, Mathoudakis L, et al. High hereditary transthyretin-related amyloidosis prevalence in Crete: genetic heterogeneity and distinct phenotypes. Neurol Genet. 2022;8(5):e200013.

Wilczek et al 2011
Wilczek HE, Larsson M, Ericzon BG. Long-term data from the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR). Amyloid. 2011;18 Suppl 1:1935.

Zeldenrust 2010
Zeldenrust SR. ATTR: diagnosis, prognosis and treatment. In: Gertz MA and Rajkumar SV, editors. Amyloidosis: diagnosis and treatment. New York, NY: Humana Press, Springer Science, Business Media LLC; 2010.

Živkovic 2020
Živkovic SA. Neuropathy associated with hereditary transthyretin amyloidosis-diagnosis and management. US Neurol. 2020;16(2):103-9.